April 28, 2000

# In a First, Gene Therapy Saves Lives of Infants

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By GINA KOLATA

For the first time, gene therapy has unequivocally succeeded, scientists say. Doctor used the treatment, which involves adding working genes to cells, to save the lives of several infants who might otherwise have died of a severe immune disorder.

AFP

French doctors Alain Fischer and Marina Cavazzana-Calvo spoke at a press conference on Thursday at Necker Children's Hospital in Paris. The doctors tested the world's first successful gene therapy treatments on four babies suffering from immunity disorders at the hospital.

The achievement, announced yesterday in France, comes after a decade of widely heralded promise followed by dashed hopes for the revolutionary treatment.

The success proves that gene therapy can work, researchers said, but the patients had a disease that is especially suited for the treatment. The researchers cautioned that the method might not be immediately applicable to other diseases.

The patients were three babies who could not grow a complete immune system. The only other treatment for the condition, a form of severe combined immune deficiency, or SCID, is a bone marrow transplant, which works just 60 percent of the time. Otherwise, patients with SCID, pronounced skid, must live in germ-free bubbles or fall prey to the ever-present microorganisms that most people can easily fend off.

In a report of the work in today's issue of the journal Science, Dr. Alain Fischer, a professor of pediatric immunology at the Hospital Necker-Enfants Malades in Paris, and his colleagues describe the course of two of the babies, 11 months and 8 months of age at the time of their treatment.

Three months after their gene therapy, the researchers recounted, the babies were home from the hospital, living like any other children. Ten months later, their immune systems were normal. Untreated infants born with SCID who are not kept in a sterile bubble become ill within months and die before their first birthday.

In a footnote, the researchers say they have now successfully treated a third baby, who was a month old at the time.

In a telephone interview, Dr. Fischer said yesterday that he had now treated two more babies and is waiting to learn whether the effort succeeded with them as well.

"We are very happy and the families are very happy," Dr. Fischer said. "It is a success today. Then the next question is, 'How long will it be a success?' It may be that after some time there will be a decline in these cells and that sooner or later we will have to treat them again. We hope that if this happens it will not be for a very long time."

Gene therapy experts were exuberant. "It's a very exciting study," said Dr. R. Michael Blaese, who was a member of a medical team at the National Institutes of Health that tried the first gene therapy on a human patient nearly 10 years ago. Dr. Blaese, now the head of the human therapeutics division at ValiGen in Newtown, Pa., added: "This would probably be the first example in any disease where gene therapy could be a fully successful treatment. You can't distinguish these patients from normal."

The success comes on the heels of a tumultuous decade in which, according to the National Institutes of Health, more than 390 gene therapy studies were initiated, involving more than 4,000 patients and more than a dozen medical conditions. While those doing the research always expressed confidence in its promise, critics said many of the companies formed to capitalize on the technology

exaggerated preliminary data in the hope of raising capital.

And, at times, some scientists promised more than the technology was ready to deliver, leaving the field a target for accusations that patients were being endangered by reckless experiments that were doomed to failure.

"We've all been so burned by saying, 'Ah, this looks like it worked, that looks like it worked,' " said Dr. W. French Anderson of the Keck School of Medicine at the University of Southern California and a member of the team that attempted the first gene therapy in 1990. "Now when it finally looks like something is working, I don't want to be in the position of saying the same words. We've all been criticized for hyping too much."

The babies treated by Dr. Fischer had a rare disorder known as severe combined immunodeficiency-X1, or SCID-X1, which almost exclusively affects boys, occurring once in every 75,000 live male births. It is caused by mutations that destroy the function of a gene that is needed to make T cells, a class of white blood cells.

In a sense, the condition is a perfect target for gene therapy. With SCID-X1, the cells that need a new gene are readily accessible in the bone marrow, whose cells are relatively easy to remove from the body.

Even better, if functioning genes actually get into the marrow cells of patients with SCID-X1, those genetically corrected cells will proliferate and displace cells with the defective gene. That is because, as the body tries to grow a complete immune system, it sends waves of chemical signals to the bone marrow to stimulate it into providing T cells.

T cells with the defective gene start to grow and then die. Any cells with a functioning gene will be fueled by the body's hormones and will grow rapidly to populate the bone marrow.

Dr. Fischer said he began working on gene therapy for SCID-X1 in 1993, as soon as the missing gene was identified. He studied the treatment for six years in mice and in the laboratory before trying to treat patients. Last year, he said, he decided "there was a serious chance that the treatment could work in this particular disease," and the success with the first babies is the result.

Scientists, of course, were well aware that SCID-X1 and other rare genetic diseases of immune system cells would be perfect for gene therapy. In fact, the very first human gene therapy patient had a similar disease.

The experiment took place at the National Institutes of Health on Sept.

14, 1990.

The problem with that experiment, Dr. Anderson said, was that researchers needed to get the new genes into stem cells, which are progenitor cells of the immune system.

But scientists at that time faced a conundrum. If they tried to put genes into stem cells that were not dividing, the cells would not accept the genes.

If they allowed the cells to divide, they would accept the genes. But, Dr. Anderson said, the cells would mature and would not be stem cells anymore.

In the past few years, this obstacle has been overcome.

Dr. Fischer said it was that advance, along with numerous technical achievements in molecular biology, that enabled him to successfully treat babies with SCID-X1.

"There is nothing new intellectually here," said Dr. Stuart Orkin, a professor of pediatrics at Harvard Medical School. "They've put together all the incremental advances that occurred over the past several years."

But many gene therapy researchers had not waited for such advances, experts said. Starting a decade ago, scientists attempted gene therapy after gene therapy in patients, trying to cure at least a dozen diseases, including cystic fibrosis, cardiovascular disease, Alzheimer's disease, hemophilia, hypercholesterolemia and -- in more than two-thirds of the studies -- cancer.

Five years ago, Dr. Orkin, as director of a federal panel reporting on gene therapy, said that there were very large numbers of clinical trials "many of which have been approved without extraordinary oversight in terms of scientific or clinical benefit."

In an interview yesterday, Dr. Orkin said: "There were a lot of people going around grandstanding and saying they could cure cystic fibrosis and many other things, which is a vast oversimplification. The awful history is not just the companies. Some of it, unfortunately, is the investigators and the academic institutions."

Last year the festering discomfort many felt with the proliferating gene therapy trials came to a head when a teenager, Jesse Gelsinger, died in a clinical trial at the University of Pennsylvania. The death brought investigations of all gene therapy studies and widespread cries that the field was moving ahead recklessly, with no success in sight.

In an interview on Wednesday, Dr. Orkin said that the panel he headed never questioned whether gene therapy would work, eventually. "What we argued for was to do the research and to look for actual clinical benefit, which hadn't been demonstrated even in a

mouse at that point."

The success, at last, of gene therapy shows the wisdom of such an approach, experts said. "They did all the science beforehand and then translated it to the patient, which is what I think the field should be doing," Dr. Orkin said.

Dr. Anderson said that while other forms of SCID should be amenable to gene therapy now, nonetheless, "because you correct SCID doesn't mean you can correct any other disease." But he added, "If you can't correct SCID, you can't correct anything else."